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ORIGINAL ARTICLE

Clinicopathological analysis and survival outcome of duodenal adenocarcinoma

Myung Jin Kim, Sae Byeol Choi*, Hyung Joon Han, Pyoung Jae Park, Wan Bae Kim, Tae Jin Song, Sung Ock Suh, Sang Yong Choi

Department of Surgery, College of Medicine, Korea University, Seoul, South Korea

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Abstract Duodenal adenocarcinoma is a rare cancer, contributing <10 % of periampullary carcinoma. This study reviews the single center experience of duodenal adenocarcinoma and analyzes the clinical and pathological factors to predict survival and recurrence. The records of 50 patients with duodenal adenocarcinoma who underwent surgical exploration or resection from 1995 to 2010 were reviewed retrospectively. Univariate and multivariate analyses were performed to identify the clinicopathological factors associated with survival and recurrence. There were 35 men and 15 women, with a mean age of 61 years. In multivariate analysis of 50 patients, R0 resection [$p = 0.041$, hazard ratio (HR) = 3.569, 95% confidence interval (CI) = 1.057–12.054] and symptom at initial admission ($p = 0.025$, HR = 11.210, 95% CI = 1.354–92.812) were independent prognostic factors for overall survival. Thirty-six patients underwent curative resection (resectability 72%). The 5-year survival rates for curative and noncurative resections were 46.4% and 0%, respectively. Univariate analysis of 36 patients who underwent R0 resection revealed that symptoms at initial admission ($p = 0.023$), presence of lymph node metastasis ($p = 0.034$), and perineural invasion ($p = 0.025$) were significant prognostic factors after curative resection. There was no significant factor for overall survival in the multivariate analysis. There was recurrence in 15 patients, mainly as liver metastasis. Multivariate analysis revealed that presence of symptom ($p = 0.047$, HR = 5.362, 95% CI = 1.021–28.149) and ulcerative tumor ($p = 0.036$, HR = 5.668, 95% CI = 1.123–28.619) were independent factors for disease free survival. An aggressive surgical approach to achieve R0 resection was important to enhance survival. Most of the recurrence occurred within 1 year after surgery. Close follow-up is necessary after surgical resection.

Conflicts of interest: All authors declare no conflicts of interest.

* Corresponding author. Department of Surgery, Korea University College of Medicine, Korea University Guro Hospital, 80, Guro-dong, Guro-gu, Seoul, South Korea.
E-mail address: csbroad@korea.ac.kr (S.B. Choi).

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Introduction

Duodenal adenocarcinoma is a rare neoplasm that comprises <0.5% of all gastrointestinal malignancies [1–3]. These neoplasms are usually grouped as periampullary carcinoma because most tumors arise in the periampullary region [3]. It is the least common, and accounts for 6% of periampullary tumors [3,4]. Because the incidence of duodenal cancer is low, most studies have been performed retrospectively with relatively few patients and a longer period of inclusion than other periampullary malignancies. Therefore, several points such as the extent of surgery including the extent of lymph node dissection and prognostic pathological factors are still controversial [1,3,5–7].

Duodenal adenocarcinoma is usually diagnosed late, because symptoms are nonspecific and resemble those of duodenal ulcer [8,9]. The surgical procedure for duodenal adenocarcinoma varies and usually depends on the location of the tumor. Segmental resection of the duodenum or pancreaticoduodenectomy is performed most commonly.

Several clinicopathological factors have been reported to affect survival for primary duodenal adenocarcinoma [1,3,5–7]. The aim of this study was to investigate the survival outcome of patients with primary duodenal adenocarcinoma and the prognostic factors affecting survival and recurrence.

Methods

From January 1995 to December 2010, 50 patients were treated for primary adenocarcinoma of duodenum at the Department of Surgery, Korea University Medical Center, Seoul, Korea. Of these patients, 36 (72%) underwent R0 resection and 14 (28%) received bypass surgery without resection (R2). We included duodenal adenocarcinoma and excluded papilla of Vater cancer.

The following demographics and clinicopathological information were reviewed retrospectively from the medical records: age, sex, comorbidities, symptoms and signs, preoperative diagnostic investigation, American Society of Anesthesiologists (ASA) class (http://www.asahq.org/clinical/physicalstatus.htm), operative procedures and time, postoperative complication, pathological results, adjuvant therapy, occurrence, and mode of recurrence.

Pathologically, the macroscopic tumor diameter was evaluated. The gross morphological features were classified into two categories: noninfiltrative versus infiltrative and nonulcerative versus ulcerative. The microscopic features investigated were differentiation, presence of perineural invasion, lymphatic invasion, lymph node metastasis, and margin status. Tumor stage was defined according to the 7th edition of pathological tumor node metastasis (pTNM) classification proposed by the American Joint Committee on Cancer (AJCC) [10]. According to the classification, T1 tumors invade the lamina propria, muscularis mucosae, or submucosa; T2 tumors invade the muscularis propria; T3 tumors invade subserosa or nonperitonealized perimuscular tissue with extension of <2 cm and T4 tumors perforate the visceral peritoneum or directly invade other organs or structures (mesentery or retroperitoneum exceeding 2 cm), and the abdominal wall or invade the pancreas. N1 disease demonstrates metastasis in one to three regional lymph nodes and N2 denotes metastasis in four or more regional lymph nodes. The regional lymph nodes for the duodenum are the pancreaticoduodenal, pyloric, hepatic, and superior mesenteric nodes.

The location of the tumor was designated according to its location in the first portion of the duodenum (D1), second portion (D2), third portion (D3), and fourth portion (D4). If the tumor involves two or more portions of the duodenum, each portion of duodenum is expressed together as follows: D12 involves the first and second portions of the duodenum, D23 involves the second and third portions, and so on. Patients who received R0 resection were classified into two groups according to the location of the tumor: D1 involved tumor versus non-D1 involved tumor, and D2 involved tumor versus non-D2 involved tumor.

Patients were followed-up at 1–2 weeks after discharge and every 3–6 months thereafter. Follow-up for duodenal cancer patients consisted of laboratory tests and imaging, such as abdominal ultrasonography and/or computed tomography (CT). Abdominal CT scan has become the main diagnostic tool for the detection of recurrence. Patients were also evaluated when recurrence was suspected.

Data are expressed as the mean ± standard deviation or median with 25th percentile and 75th percentile for continuous variables. Statistical analysis was performed using SPSS, version 13.0 for Windows (SPSS Inc., Chicago, IL, USA). Survival was measured from the date of operation. Follow-up of patients was completed when death occurred or until August 31, 2012. Disease-free survival (DFS) was measured from the date of surgery to diagnosis of recurrence. Survival was calculated by the Kaplan–Meier method. Clinicopathological factors were analyzed by the univariate Kaplan–Meier method and compared by the log-rank test to identify significant prognostic predictors for overall survival and DFS. Multivariate analysis using the Cox proportional hazards model was performed to identify the independent prognostic predictors for overall survival. Comparisons between groups were tested using the Pearson Chi-square test. A p value <0.05 was considered statistically significant.

Results

Clinical characteristics

The patients comprised 35 men and 15 women with a mean age of 61 years (range, 38–82 years). The chief complaint at admission was abdominal pain (n = 21), vomiting (n = 9), gastrointestinal bleeding (n = 8), dyspepsia (n = 8), weight loss (n = 5), jaundice (n = 3), diarrhea (n = 1), and edema (n = 1). Seven patients were diagnosed as duodenal cancer asymptomatically by general medical check-up. All patients were suspected duodenal cancer preoperatively. Of the 50 patients, 48 received esophagogastroscopy, which was diagnostic of duodenal cancer in 45 patients. Endoscopic biopsy was performed in 47 patients. The results were adenocarcinoma (n = 29), adenoma (n = 5), inflammation (n = 7), and atypical cell or dysplasia (n = 5). CT scans were acquired in 47 patients and were diagnostic of duodenal cancer in 32 patients.

The patients were classified by ASA class as ASA 1 ($n = 9$), ASA 2($n = 36$), and ASA 3 ($n = 5$). Of the 50 patients, 36 received curative resection (resectability 72%). The operative procedure according to the location of tumor is summarized in Table 1. The main procedure was pancreaticoduodenectomy, classic Whipple's operation in 18 patients and pylorus-preserving pancreaticoduodenectomy in 13 patients. The choice of operation was determined according to the location of the tumor. Combined resection of other organs was performed in nine patients and involved right hemicolectomy ($n = 3$), segmental resection of transverse colon ($n = 2$), liver resection ($n = 1$), radical cholecystectomy ($n = 1$), and portal vein resection and anastomosis ($n = 2$). The mean operation time was 367 minutes for curative resection. Fourteen patients received R2 resection (bypass surgery for palliation in 13 patients and exploration in 1 patient) due to a locally advanced and unresectable tumor ($n = 9$), peritoneal seeding ($n = 4$), and distant metastasis ($n = 6$).

Postoperative complications occurred in 22 patients (morbidity 44%), which most commonly was intra-abdominal abscess ($n = 14$) associated with postoperative pancreatic fistula in pancreaticoduodenectomy. Other complications were pulmonary complications ($n = 6$), bleeding ($n = 4$), delayed gastric emptying ($n = 3$), superficial surgical site infection ($n = 3$), and congestive heart failure ($n = 1$). Postoperative mortality occurred in three patients whose causes of death were septic shock after curative surgery ($n = 2$) and exacerbation of underlying congestive heart failure ($n = 1$) after laparoscopic gastrojejunostomy for palliation, representing an overall mortality rate of 6%.

Adjuvant chemotherapy was performed in 21 patients, usually based on 5-fluoruracil monotherapy or 5-fluorouracil combined with cisplatin.

Overall survival and clinicopathological factors affecting survival

Of the 50 patients with duodenal carcinoma, the overall survival rate was 38.8% at 3 years and 32.3% at 5 years, with a median survival time of 24.4 months. R0 resection ($p < 0.001$), symptom at initial admission ($p = 0.012$), hyperbilirubinemia ($p = 0.020$), ASA class ($p < 0.001$), T

Table 1 Operative procedures according to the location of tumor.

	D1	D2	D3	D12	D23	D34	Total
PD	4	9	1	2	2		18
PPPD	1	10			2		13
Transduodenal excision		1					1
Segmental resection			1			1	2
SGD	2						2
Total	7	20	2	2	4	1	36

PD = pancreaticoduodenectomy; PPPD = pylorus-preserving pancreaticoduodenectomy; SGD = subtotal gastrectomy with segmental resection of duodenum.

Table 2 Univariate analysis of prognostic factors for overall survival in 50 patients with duodenal cancer.

Prognostic factors		No. of patients	5YSR (%)	*p*
Curativity	R0	36	46.4	<0.001
	R2	14	0	
Age (y)	<60	22	45.8	0.145
	≥60	28	17.6	
Sex	M	35	30.5	0.797
	F	15	36.9	
Symptom	Asymptomatic	7	80	0.012
	Symptomatic	43	23.9	
Hyperbilirubinemia	No	42	37.2	0.020
	Yes	8	0	
Anemia	No	33	39.5	0.127
	Yes	17	18.1	
ASA class	I	9	66.7	<0.001
	II	36	23.0	
	III	5	0	
T stage[a]	T1,T2,T3	10	85.7	0.026
	T4	35	26.9	
TNM stage[b]	I	7	55.6	0.001
	II	16	48.8	
	III	18	25.6	
	IV	8	0	
Adjuvant therapy	No	29	18	0.046
	Yes	21	49.2	

5YSR = 5-year survival rate; ASA = American Society of Anesthesiologists; TNM = tumor node metastasis.
[a] Five patients had unknown T stage due to bypass surgery.
[b] One patient received laparoscopic gastrojejunostomy due to severe comorbidity and old age, therefore exact stage was unknown.

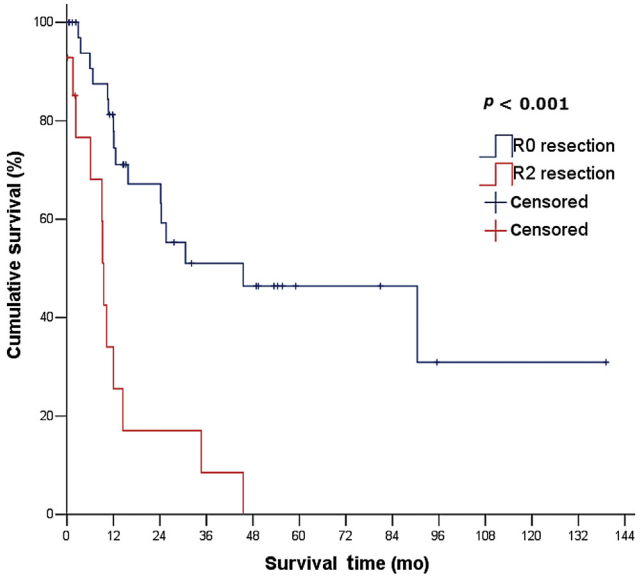

Figure 1. The overall survival was significantly different according to R status ($p < 0.001$). Five-year survival of R0 resection group was 46.4%, and R2 resection group was 0%.

stage ($p = 0.026$), TNM stage ($p = 0.001$), and adjuvant chemotherapy ($p = 0.046$) were significant factors for overall survival rate in the univariate analysis (Table 2). In multivariate analysis, R0 resection [$p = 0.041$, hazard ratio (HR) = 3.569, 95% confidence interval (CI) = 1.057–12.054] and symptom at initial admission ($p = 0.025$, HR = 11.210, 95% CI = 1.354–92.812) were independent prognostic factors for overall survival.

Of the 36 patients who underwent R0 resection, the overall survival rate was 46.4% at 5 years (Fig. 1). Symptom at initial admission ($p = 0.023$), perineural invasion ($p = 0.025$), and lymph node metastasis ($p = 0.034$) were significant prognostic factors for overall survival in univariate analysis. Ulceration and infiltration of tumor, differentiation, location of tumor, T stage, and TNM stage did not affect overall survival significantly (Table 3). However, in multivariate analysis, there was no significantly independent prognostic factor for overall survival after curative resection.

Recurrence and clinicopathological factors affecting disease-free survival

Recurrence after curative resection of duodenal cancer was detected in 15 patients. Fourteen patients did not demonstrate recurrent disease during the follow-up period, and the status of eight patients was unknown. The site of recurrence was locoregional in three patients, liver metastasis in 10 patients, lymph node metastasis in five patients, and peritoneal seeding in three patients. Only one patient showed solitary locoregional recurrence. Treatments for recurrent disease was performed in 10 patients, and were systemic chemotherapy ($n = 6$), concurrent

Table 3 Univariate analysis of prognostic factors for overall survival in 36 patients with duodenal cancer who received R0 resection.

Prognostic factors		No. of patients	5YSR (%)	*p*
Age (y)	<60	16	62.5	0.251
	≥60	20	25.7	
Sex	M	25	45.4	0.742
	F	11	48.6	
Symptom	Asymptomatic	6	100	0.023
	Symptomatic	30	35.3	
Hyperbilirubinemia	No	31	51.4	0.111
	Yes	5	0	
Anemia	No	26	51.3	0.45
	Yes	10	33.3	
ASA class	I	8	75	0.136
	II	28	31.7	
Size of tumor (cm)	≤3	15	45.7	0.535
	>3	21	46.5	
Ulceration of tumor	Nonulcerative	17	59.7	0.576
	Ulcerative	19	35.5	
Infiltration of tumor	Noninfiltrative	19	62.5	0.084
	Infiltrative	17	23.9	
Differentiation	Well	11	64.6	0.125
	Moderate and poor	25	38.5	
Lymphatic invasion	No	29	48.4	0.062
	Yes	7	40	
Perineural invasion	No	26	55.5	0.025
	Yes	10	18.5	
Lymph node metastasis	No	21	60.8	0.034
	Yes	15	27.8	
Involvement of D1	No	27	45.6	0.810
	Yes	9	50	
Involvement of D2	No	10	66.7	0.273
	Yes	26	34.9	
T stage	T1,T2,T3	10	85.7	0.071
	T4	26	36.0	
TNM stage	I	7	55.6	0.082
	II	16	57.1	
	III	13	28.6	
Adjuvant therapy	No	18	27	0.386
	Yes	18	62.3	

5YSR = 5-year survival rate; ASA = American Society of Anesthesiologists; TNM = tumor node metastasis.

chemoradiation therapy ($n = 3$), and cryotherapy for metastatic liver tumor ($n = 1$).

The overall DFS rates were 60.3% at 1 year and 31.3% at 3 years. Median DFS time was 15.4 months and 10 patients demonstrated recurrence within 1 year after curative resection. Univariate analysis of clinicopathological predictors for DFS showed that presence of symptom at initial admission ($p = 0.045$) was a significant factor; however, lymph node metastasis ($p = 0.052$) demonstrated poor DFS with marginal significance. In multivariate analysis, the presence of symptom ($p = 0.047$, HR 5.362, 95% CI 1.021−28.149) and ulcerative tumor ($p = 0.036$, HR 5.668, 95% CI 1.123−28.619) were independent factors for DFS.

Discussion

In the current study, duodenal adenocarcinoma was diagnosed at an advanced stage. More than two-thirds of patients who underwent curative resection were categorized as T4. To achieve R0 resection, pancreaticoduodenectomy with a combined operation involving the cancer-invaded organ was performed frequently. Survival was significantly improved for patients who underwent curative resection rather than palliative surgery. The resectability rate has been reported as 53−67%. Performance of curative resection is the strongest determinant of outcome [3,7,11]. An aggressive surgical approach to achieve complete tumor removal should be performed.

The diagnostic rate seemed to be low at the preoperative stage: endoscopically proven malignancy was 29 among 47 patients, and there were 32 suspected duodenal cancers among 47 patients who had CT scans in the current study. If malignancy was suspected, but not proven by endoscopic biopsy or CT preoperatively, surgical exploration with intraoperative frozen biopsy could be an option. In those cases, malignancy favored extensive curative resection and bypass surgery for benign stricture, and limited surgical resection with free margin of tumor could be performed in the case of adenoma.

Lymph node metastasis is one of the most significant prognostic factors in duodenal carcinoma [1,5−7], and was also apparent in the present study. The risk of lymph node metastasis increases with T stage, and 5-year survival decreases as the number of metastatic lymph nodes increases, which seems to be significantly poorer when more than four lymph nodes are metastasized or more than 20% of the retrieved nodes are invaded by tumors [6]. Other authors have reported that the presence of lymph node metastasis is not a significant prognostic factor and the location of the involved nodes does not influence outcome [3,5,11,12]. Therefore, they emphasized the aggressive surgical role to enhance survival outcome, although lymph node metastasis was present.

Prognostic factors, such as weight loss, surgical type, tumor location, presence of perineural invasion, resection margin status, and tumor grade and stage, remain controversial in terms of whether or not they might impact on survival in the review of literature [1,3,5,6,8,11−13]. In the current study, presence of symptom and ulcerative tumor were independent factors for DFS rather than factors associated with tumor stage. This might be because the number of patients included in this study was small and most of the patients were T4 (26 patients/36 patients), and most were TNM stage II or III. Therefore, pathological factors including stage were not a significant factor for disease free survival in the multivariate analysis.

Duodenal adenocarcinoma seems to be more biologically comparable to gastric cancer rather than pancreatic adenocarcinoma [11]. The choice of procedure was determined according to the location of the tumor. Usually, segmental resection is appropriate for patients with lesions of the distal duodenum. For D1 and D2 lesions, pancreaticoduodenectomy is required [1]. No difference has been found in the survival rates between patients undergoing segmental resection and pancreaticoduodenectomy [1,5]. However, other authors have reported a survival difference according to the operative procedure. Pancreaticoduodenectomy was more beneficial to overall survival than pancreas-sparing duodenectomy, and D1 and D2 tumors demonstrated better survival than D3 and D4 tumors [3].

Recent studies have reported that adjuvant chemoradiotherapy does not decrease local recurrence or prolong overall survival [1,2,6]. However, adjuvant chemoradiation therapy is used more commonly for patients with nodal metastasis [6], and might enhance locoregional control in the advanced stage of duodenal cancer following curative resection [2]. The pattern of recurrence after curative resection is mainly distant, and the most common site of distant metastasis is the liver [1,6,13]. Although presently locoregional control of duodenal adenocarcinoma could be achieved most often by pancreaticoduodenectomy and combined operation involving the invaded organ, systemic control to prevent disease progression remains to be solved. In the current study, adjuvant chemotherapy did not affect overall survival and DFS following curative resection. However, systemic chemotherapy was effective in improving survival outcome after curative or palliative surgery. Because most studies have been performed on retrospectively with a relatively small number of patients, and adjuvant chemotherapy tends to be delivered in advanced cases [6], the chemotherapeutic agent and regimen were not homogeneous. Further studies will be necessary to investigate the role of adjuvant chemo- and/or radiotherapy to achieve systemic as well as locoregional control of duodenal adenocarcinoma in a prospective clinical trial.

In conclusion, duodenal adenocarcinoma was diagnosed at an advanced stage, and the resectability was low. Curative resection enhanced survival, indicating that a vigorous surgical approach with combined resection of the invaded organ should be pursued. Lymph node metastasis was a significant prognostic factor affecting survival. Recurrence was diagnosed within 1 year after curative resection in two-thirds of the recurrent patients, mainly as distant metastasis. Therefore, a careful follow-up program with short-term interval should be applied and adjuvant chemoradiotherapy might be considered in an advanced disease, although the impact of adjuvant therapy affecting survival was not obvious. Further studies will be necessary to investigate the effect of adjuvant therapy for duodenal adenocarcinoma in a prospective clinical trial.

References

[1] Bakaeen FG, Murr MM, Sarr MG, Thompson GB, Farnell MB, Nagorney DM, et al. What prognostic factors are important in duodenal adenocarcinoma? Arch Surg 2000;135:635—41. discussion 641—2.

[2] Kim K, Chie EK, Jang JY, Kim SW, Oh DY, Im SA, et al. Role of adjuvant chemoradiotherapy for duodenal cancer: a single center experience. Am J Clin Oncol 2012;35:533—6.

[3] Sohn TA, Lillemoe KD, Cameron JL, Pitt HA, Kaufman HS, Hruban RH, et al. Adenocarcinoma of the duodenum: factors influencing long-term survival. J Gastrointest Surg 1998;2:79—87.

[4] Okada K, Fujisaki J, Kasuga A, Omae M, Kubota M, Hirasawa T, et al. Sporadic nonampullary duodenal adenoma in the natural history of duodenal cancer: a study of follow-up surveillance. Am J Gastroenterol 2011;106:357—64.

[5] Rotman N, Pezet D, Fagniez PL, Cherqui D, Celicout B, Lointier P. Adenocarcinoma of the duodenum: factors influencing survival. French Association for Surgical Research. Br J Surg 1994;81:83—5.

[6] Poultsides GA, Huang LC, Cameron JL, Tuli R, Lan L, Hruban RH, et al. Duodenal adenocarcinoma: clinicopathologic analysis and implications for treatment. Ann Surg Oncol 2012;19:1928—35.

[7] Lee HG, You DD, Paik KY, Heo JS, Choi SH, Choi DW. Prognostic factors for primary duodenal adenocarcinoma. World J Surg 2008;32:2246—52.

[8] Chung WC, Paik CN, Jung SH, Lee KM, Kim SW, Chang UI, et al. Prognostic factors associated with survival in patients with primary duodenal adenocarcinoma. Korean J Intern Med 2011; 26:34—40.

[9] Hung FC, Kuo CM, Chuah SK, Kuo CH, Chen YS, Lu SN, et al. Clinical analysis of primary duodenal adenocarcinoma: an 11-year experience. J Gastroenterol Hepatol 2007;22:724—8.

[10] Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, editors. AJCC Cancer staging manual. 7th ed. New York: Springer-Verlag; 2009.

[11] Rose DM, Hochwald SN, Klimstra DS, Brennan MF. Primary duodenal adenocarcinoma: a ten-year experience with 79 patients. J Am Coll Surg 1996;183:89—96.

[12] Ryder NM, Ko CY, Hines OJ, Gloor B, Reber HA. Primary duodenal adenocarcinoma: a 40-year experience. Arch Surg 2000;135:1070—4. discussion 1074—5.

[13] Struck A, Howard T, Chiorean EG, Clarke JM, Riffenburgh R, Cardenes HR. Non-ampullary duodenal adenocarcinoma: factors important for relapse and survival. J Surg Oncol 2009;100: 144—8.